KEPIVANCE - palifermin injection
Amgen

DESCRIPTION

Kepivance (palifermin) is a human keratinocyte growth factor (KGF) produced by recombinant DNA technology in *Escherichia coli* (*E coli*). Kepivance is a water-soluble, 140 amino acid protein with a molecular weight of 16.3 kilodaltons. It differs from endogenous human KGF in that the first 23 N-terminal amino acids have been deleted to improve protein stability.
Kepivance is supplied as a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 mL of Sterile Water for Injection, USP. Reconstitution yields a clear, colorless solution of Kepivance (5 mg/mL) with a pH of 6.5. Each single-use vial of Kepivance contains 6.25 mg palifermin, 50 mg mannitol, 25 mg sucrose, 1.94 mg L-histidine, and 0.13 mg polysorbate 20 (0.01% w/v).

CLINICAL PHARMACOLOGY

Mechanism of Action

Keratinocyte growth factor (KGF) is an endogenous protein in the fibroblast growth factor (FGF) family that binds to the KGF receptor. Binding of KGF to its receptor has been reported to result in proliferation, differentiation, and migration of epithelial cells. The KGF receptor, one of four receptors in the FGF family, has been reported to be present on epithelial cells in many tissues examined including the tongue, buccal mucosa, esophagus, stomach, intestine, salivary gland, lung, liver, pancreas, kidney, bladder, mammary gland, skin (hair follicles and sebaceous gland), and the lens of the eye. The KGF receptor has been reported to not be present on cells of the hematopoietic lineage. Endogenous KGF is produced by mesenchymal cells and is upregulated in response to epithelial tissue injury.
In mice and rats, Kepivance enhanced proliferation of epithelial cells (as measured by Ki67 immunohistochemical staining and BrDU uptake) and demonstrated an increase in tissue thickness of the tongue, buccal mucosa, and gastrointestinal tract. Kepivance has been studied in murine models of chemotherapy and radiation-induced gastrointestinal injury. In such models, administration of Kepivance prior to and/or after the cytotoxic insult improved survival and reduced weight loss compared to control animals.
Kepivance has been shown to enhance the growth of human epithelial tumor cell lines in vitro at concentrations ≥ 10 mcg/mL (> 15-fold higher than average therapeutic concentrations in humans). In nude mouse xenograft models, three consecutive daily treatments of Kepivance at doses of 1,500 and 4,000 mcg/kg (25- and 67-fold higher than the recommended human dose, respectively) repeated weekly for 4 to 6 weeks were associated with a dose-dependent increase in the growth rate of 1 of 7 KGF receptor-expressing human tumor cell lines.

Pharmacokinetics

The pharmacokinetics of Kepivance were studied in healthy subjects and patients with hematologic malignancies. After single IV doses of 20 to 250 mcg/kg (healthy subjects) and 60 mcg/kg (cancer patients), Kepivance concentrations declined rapidly (over 95% decrease) in the first 30 minutes post-dose. A slight increase or plateau in concentration occurred at approximately 1 to 4 hours, followed by a terminal decline phase. Kepivance exhibited linear pharmacokinetics with extravascular distribution. On average, total body clearance (CL) appeared to be 2- to 4-fold higher, and volume of distribution at steady state (Vss) to be 2-fold higher in cancer patients compared with healthy subjects after a 60 mcg/kg single dose of Kepivance. The elimination half-life was similar between healthy subjects and cancer patients (average 4.5 hours with a range of 3.3 to 5.7 hours). No accumulation of Kepivance occurred after 3 consecutive daily doses of 20 and 40 mcg/kg in healthy volunteers or 60 mcg/kg in cancer patients.

Pharmacodynamics

Epithelial cell proliferation was assessed by Ki67 immunohistochemical staining in healthy subjects. A 3-fold or greater increase in Ki67 staining was observed in buccal biopsies from 3 of 6 healthy subjects given Kepivance at 40 mcg/kg/day IV for 3 days, when measured 24 hours after the third dose. Dose-dependent epithelial cell proliferation was observed in healthy subjects given single IV doses of 120 to 250 mcg/kg 48 hours post-dosing.

Special Populations

No gender-related differences were observed in the pharmacokinetics of Kepivance at doses ≤ 60 mcg/kg. The pharmacokinetic profile in pediatric populations (see **PRECAUTIONS: Pediatric Use**), or in patients with hepatic insufficiency, has not been assessed.
Geriatric Use: No age-related differences were observed in the pharmacokinetics of Kepivance ≤ 180 mcg/kg. (see **PRECAUTIONS: Geriatric Use**)
Renal Impairment: Results from a pharmacokinetics study in 24 subjects with varying degrees of renal impairment demonstrated that renal impairment has little or no influence on Kepivance pharmacokinetics. No dose adjustment is recommended for patients with renal impairment.

CLINICAL STUDIES

The safety and efficacy of Kepivance were established in a randomized placebo-controlled clinical study of 212 patients (Study 1) and a randomized, schedule-ranging, placebo-controlled clinical study of 169 patients (Study 2).

In Study 1, patients received high-dose cytotoxic therapy consisting of fractionated total-body irradiation (TBI) (12 Gy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (100 mg/kg) followed by peripheral blood progenitor cell (PBPC) support for the treatment of hematological malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma). Patients were randomized to receive either Kepivance (n = 106) or placebo (n = 106). Kepivance was administered as a daily IV injection of 60 mcg/kg for 3 consecutive days prior to initiation of cytotoxic therapy and for 3 consecutive days following infusion of PBPC.

The main efficacy endpoint of Study 1 was the number of days during which patients experienced severe oral mucositis (Grade 3/4 on the WHO [World Health Organization] scale).[1] Other endpoints included the incidence, duration, and severity of oral mucositis and the requirement for opioid analgesia. There was no evidence of a delay in time to hematopoietic recovery in patients who received Kepivance as compared to patients who received placebo.

The efficacy results are presented in Table 1 and Figure 1.

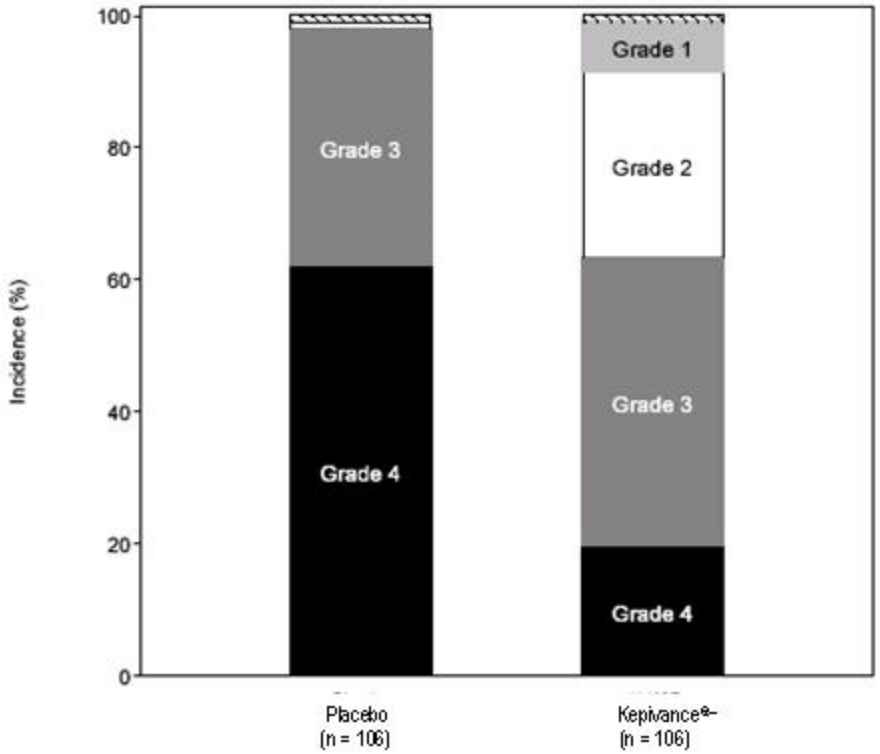
Table 1. Efficacy Outcomes in Study 1

	Kepivance (60 mcg/kg/day) (n = 106)	**Placebo (n = 106)**
Median* (25th, 75th percentile) Days of WHO Grade 3/4 Oral Mucositis†	3 (0, 6)	9 (6, 13)
Incidence of WHO Grade 3/4 Oral Mucositis	63% (67/106)	98% (104/106)
Median (25th, 75th percentile) Days of WHO Grade 3/4 Oral Mucositis in Affected Patients	6 (3, 8) (n = 67)	9 (6, 13) (n = 104)
Incidence of WHO Grade 4 Oral Mucositis	20%	62%
Median (25th, 75th percentile) Days of WHO Grade 2/3/4 Oral Mucositis	8 (4, 12)	14 (11, 19)
Opioid Analgesia for Oral Mucositis: Median (25th, 75th percentile) Days Median (25th, 75th percentile) Cumulative Dose (morphine mg equivalents)	7 (1, 10) 212 (3, 558)	11 (8, 14) 535 (269, 1429)

*****P < 0.001 compared to placebo, using Generalized Cochran-Mantel-Haenszel (CMH) test stratified for study center. P-values presented for primary endpoint only.

†WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible.

Figure 1. Incidence of Oral Mucositis by Maximum Grade in Study 1



WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible.

In Study 1, patients used a daily diary to record the amount of mouth and throat soreness. Compared with placebo-treated patients, Kepivance-treated patients reported less mouth and throat soreness.

Study 2 was a randomized, multi-center, placebo-controlled study comparing varying schedules of Kepivance. All patients received high-dose cytotoxic therapy consisting of fractionated TBI (12cGy total dose), high-dose etoposide (60 mg/kg), and high-dose cyclophosphamide (75-100 mg/kg) followed by PBPC support for the treatment of hematological malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma).

The results of Study 1 were supported by results observed in the subset of patients in Study 2 who received the same dose and schedule of Kepivance as given in Study 1. Compared with placebo, there was a reduction in median days of WHO Grade 3/4 oral mucositis (4 vs 6 days), lower incidence of WHO Grade 3/4 oral mucositis (67% vs 80%) and lower incidence of WHO Grade 4 oral mucositis (26% vs. 50%) for Kepivance.

The results of Study 1 were supported by results observed in the subset of patients in Study 2 who received the same dose and schedule of Kepivance as given in Study 1. Compared with placebo, there was a reduction in median days of WHO Grade 3/4 oral mucositis (4 vs 6 days), lower incidence of WHO Grade 3/4 oral mucositis (67% vs 80%) and lower incidence of WHO Grade 4 oral mucositis (26% vs. 50%) for Kepivance.

One of the schedules tested in Study 2 randomized patients to receive Kepivance for 3 consecutive days prior to initiation of cytotoxic therapy, a dose given on the last day of TBI prior to etoposide, and for 3 consecutive days following infusion of PBPC. This arm was prematurely closed by the Safety Committee after enrollment of 35 patients due to lack of efficacy and a trend towards increased severity and duration of oral mucositis as compared to placebo-treated patients. This finding was attributed to administration of Kepivance within 24 hours of chemotherapy, resulting in an increased sensitivity of the rapidly dividing epithelial cells in the immediate post-chemotherapy period (see **PRECAUTIONS: Drug Interactions** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Kepivance is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

The safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies (see **PRECAUTIONS**).

CONTRAINDICATIONS

Kepivance is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, palifermin, or any other component of the product.

PRECAUTIONS

Potential for Stimulation of Tumor Growth

The safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies. The effects of Kepivance on stimulation of KGF receptor-expressing, non-hematopoietic tumors in patients are not known. Kepivance has been shown to enhance the growth of human epithelial tumor cell lines in vitro and to increase the rate of tumor cell line growth in a human carcinoma xenograft model (see **CLINIAL PHARMACOLOGY, Mechanism of Action**).

Information for Patients

Patients should be informed of the possible adverse effects of Kepivance, including muco-cutaneous adverse effects. These include rash, erythema, edema, pruritus, oral/perioral dysesthesia, tongue discoloration, tongue thickening, and alteration of taste. Patients should be instructed to report these adverse effects, or any other adverse reactions, to the prescribing physician (see **ADVERSE REACTIONS**).

The safety and efficacy of Kepivance have not been established in patients with non-hematologic malignancies. Patients should be informed of the evidence of tumor growth and stimulation in cell culture and in animal models of non-hematopoietic human tumors.

Drug Interactions

In-vitro and in vivo data suggests that palifermin interacts with unfractionated as well as low molecular weight heparins. While the clinical relevance is unclear, heparin should be used with care in patients who are concomitantly administered palifermin. Therefore, if heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after Kepivance administration.

Kepivance should not be administered within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy (see **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**). In a clinical trial, administration of Kepivance within 24 hours of chemotherapy resulted in increased severity and duration of oral mucositis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity: In a study to assess potential carcinogenicity in transgenic rasH2 mice, no treatment related increases in the incidence of neoplastic lesions were observed.

Mutagenicity: No clastogenic or mutagenic effects of Kepivance were observed in the Ames or mammalian chromosomal aberration assays; however, such studies are generally not informative for biological products.

Impairment of Fertility: When Kepivance was administered intravenously daily to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected at doses up to 100 mcg/kg/day. Systemic toxicity (clinical signs of toxicity and/or body weight effects), decreased epididymal sperm counts, and increased post-implantation losses were observed at doses ≥ 300 mcg/kg/day (5-fold higher than the recommended human dose). Increased pre-implantation loss and a decreased fertility index were observed at a Kepivance dose of 1000 mcg/kg/day.

Pregnancy Category C

Kepivance has been shown to be embryotoxic in rabbits and rats when given in doses that are 2.5 and 8 times the human dose, respectively.

Increased post-implantation loss and decreased fetal body weights were observed when Kepivance was administered to pregnant rabbits from days 6 to 18 of gestation at IV doses ≥ 150 mcg/kg/day (2.5-fold higher than the recommended human dose). However, treatment with these doses was also associated with maternal toxicity (clinical signs and reductions in body weight gain/food consumption). No evidence of developmental toxicity was observed in rabbits at doses up to 60 mcg/kg/day.

Increased post-implantation loss, decreased fetal body weight, and/or increased skeletal variations were observed when Kepivance was administered to pregnant rats from days 6 to 17 or 19 of gestation at IV doses ≥ 500 mcg/kg/day (> 8-fold higher than the recommended human dose). Treatment with these doses was also frequently associated with maternal toxicity (clinical signs and body weight effects). No evidence of developmental toxicity was observed in rats at doses up to 300 mcg/kg/day.

There are no adequate and well-controlled studies in pregnant women. Kepivance should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactating Women

It is not known whether Kepivance is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Kepivance is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Kepivance in pediatric patients have not been established.

Geriatric Use
A single dose IV study of palifermin (90 or 180 mcg/kg) conducted in healthy volunteers age 18-80 indicates that age does not have clinically meaningful effects on the pharmacokinetics of palifermin.

ADVERSE REACTIONS
Please refer to the **PRECAUTIONS: Potential for Stimulation of Tumor Growth** and **CLINICAL PHARMACOLOGY: Mechanism of Action** sections regarding the potential for tumor stimulatory effects in KGF receptor-expressing tumors.

Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.
Safety data are based upon 409 patients with hematologic malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma) who received Kepivance and 241 patients who received placebo in 3 randomized, placebo-controlled clinical studies and a pharmacokinetic study. Patients received Kepivance either before, or before and after, regimens of myelotoxic chemotherapy, with or without TBI, followed by PBPC support. The patients were predominantly between the ages of 41 and 60 years (median 48 yrs), male (62%), white (83%). NHL was the most common malignancy followed by Hodgkin's disease, multiple myeloma, and leukemia.
The most common serious adverse reaction attributed to Kepivance was skin rash, which was reported in less than 1% (3/409) of patients treated with Kepivance. Grade 3 skin rashes occurred in 14 patients, 9 of 409 (3%) receiving Kepivance and 5 of 241 (2%) receiving placebo. In seven patients (5 Kepivance, 2 placebo), study drug was discontinued due to skin rash. Other serious adverse reactions occurred at a similar rate in patients who received Kepivance (20%) or placebo (21%). The most frequently reported serious adverse events in Kepivance and placebo-treated patients were fever, gastrointestinal events, and respiratory events.
The most common adverse reactions attributed to Kepivance were skin toxicities (rash, erythema, edema, pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, alteration of taste), pain arthralgias, and dysesthesia. The median time to onset of cutaneous toxicity was 6 days following the first of 3 consecutive daily doses of Kepivance, with a median duration of 5 days.
In patients receiving Kepivance, dysesthesia (including hyperesthesia, hypoesthesia, and paresthesia) was usually localized to the perioral region, whereas in patients receiving placebo dysesthesias were more likely to occur in extremities. Adverse events occurring more frequently in Kepivance-treated patients as compared to placebo-treated patients (a higher incidence of ≥ 5%) are listed in Table 2.

Table 2. Adverse Events Occurring With ≥ 5% Higher Incidence in Kepivance vs. Placebo

BODY SYSTEM Adverse Event	Kepivance (n = 409)	Placebo (n = 241)
BODY AS A WHOLE		
Edema	28%	21%
Pain	16%	11%
Fever	39%	34%
GASTROINTESTINAL		
Mouth/Tongue Thickness or Discoloration	17%	8%
MUSCULOSKELETAL		
Arthralgia	10%	5%
SKIN AND APPENDAGES		
Rash	62%	50%
Pruritus	35%	24%
Erythema	32%	22%
SPECIAL SENSES		
Taste Altered	16%	8%

CNS/PNS		
Dysesthesia – Hyperesthesia / hypoesthesia / paresthesia	12%	7%
METABOLIC		
Elevated serum lipase (Grade 3/4)	28% (11%)	23% (5%)
Elevated serum amylase (Grade 3/4)	62% (38%)	54% (31%)

Hypertension: In a phase 1 placebo-controlled study in patients undergoing hematopoietic transplantation and receiving Kepivance (3 doses pre-myelotoxic therapy and 3 doses post-transplant), the proportion of Kepivance-treated patients reporting an adverse event of hypertension in the 60- and 80-mcg/kg/day Kepivance cohorts was greater than in the placebo group (2/15 patients [13%], 2/14 [14%], and 2/23 [9%], respectively). These events were transient and did not require treatment discontinuation in any patient. In an integrated analysis of adverse events across Kepivance studies in the hematology transplant setting, hypertensive events were reported in 30/409 Kepivance (7%) patients and 13/241 placebo (5%) patients.
Proteinuria: In a placebo-controlled study conducted in 145 patients with metastatic colorectal cancer receiving multi-cycle chemotherapy (5-FU/leucovorin), serial urine specimens were collected for 27 placebo-treated and 54 Kepivance-treated patients. Among the 54 Kepivance-treated patients, 9 patients with a baseline urinalysis negative for protein subsequently developed 2+ or greater proteinuria after treatment with Kepivance. Among the 27 placebo-treated patients evaluated, none developed 2+ or greater proteinuria. Because of the study design, the number of cycles with urine analysis data collected was higher in the Kepivance- treated patients. In addition, for the 9 patients with proteinuria, underlying medical conditions known to be associated with proteinuria were present at baseline. A causal relationship between Kepivance and proteinuria has not been established.
Laboratory Values: Reversible elevations in serum lipase and amylase, which did not require treatment intervention, are shown in Table 2. In general, peak increases were observed during the period of cytotoxic therapy and returned to baseline by the day of PBPC infusion. Fractionation of amylase revealed it to be predominantly salivary in origin.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The clinical significance of antibodies to Kepivance is unknown but may include lessened activity and/or cross reactivity with other members of the FGF family of growth factors.
A sensitive electrochemiluminescence-based binding assay was performed on post-treatment sera from 645 patients treated with Kepivance in clinical studies. Twelve (2%) of these 645 patients tested positive for antibodies to Kepivance following treatment. None of the samples had evidence of neutralizing activity in a cell-based assay.
The incidence of antibody positivity is highly dependent on the specific assay and its sensitivity. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Kepivance with the incidence of antibodies to other products may be misleading.

Postmarketing Experience
The following adverse reactions have been identified during postapproval of Kepivance. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
The following adverse reactions have been identified during postmarketing use of Kepivance in the stem cell transplant setting: tongue disorder (e.g. redness, bumps, edema); face edema and mouth edema; vaginal edema and erythema; transient hyperpigmentation of the skin; Palmar-plantar Erythrodysaesthesia Syndrome (dysaesthesia, erythema, edema on the palms and soles) and anaphylactic / allergic reactions.

OVERDOSAGE
The maximum amount of Kepivance that can be safely administered in a single dose has not been determined. Single doses of 250 mcg/kg have been administered intravenously to 8 healthy volunteers without severe or serious adverse effects. Five of 14 patients receiving six doses of 80 mcg/kg/day administered intravenously over 2 weeks (three doses preceding and three doses following myeloablative chemotherapy/TBI) experienced serious or severe adverse events. These events were consistent with those observed at the recommended dose but were generally more severe.

DOSAGE AND ADMINISTRATION
The recommended dosage of Kepivance is 60 mcg/kg/day, administered as an IV bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses.
Pre-myelotoxic therapy: The first 3 doses should be administered prior to myelotoxic therapy, with the third dose 24 to 48 hours before myelotoxic therapy (see **PRECAUTIONS: Drug Interactions**).
Post-myelotoxic therapy: The last 3 doses should be administered post-myelotoxic therapy; the first of these doses should be administered after, but on the same day of hematopoietic stem cell infusion and at least 4 days after the most recent administration of Kepivance (see **PRECAUTIONS: Drug Interactions**).

No dose adjustment is recommended for patients with renal impairment (see **CLINICAL PHARMACOLOGY: Special Populations**).

Preparation of Kepivance

Do not use Kepivance beyond the date stamped on the vial label.

Kepivance lyophilized powder should only be reconstituted with Sterile Water for Injection, USP (not supplied). Kepivance should be reconstituted aseptically by slowly injecting 1.2 mL of Sterile Water for Injection, USP (not supplied) to yield a final concentration of 5 mg/mL. The contents should be swirled gently during dissolution. **Do not shake or vigorously agitate the vial**.

Generally, dissolution of Kepivance takes less than 3 minutes.

PROTECT FROM LIGHT

The reconstituted solution contains no preservatives and is intended for single use only. Following reconstitution, it is recommended that the product be used immediately. If not used immediately, the reconstituted solution of Kepivance may be stored refrigerated in its carton at 2° to 8°C (36° to 46°F) for up to 24 hours. Prior to injection, Kepivance may be allowed to reach room temperature for a maximum of 1 hour but should be protected from light. Discard Kepivance left at room temperature for more than 1 hour. Do not freeze the reconstituted solution.

The reconstituted solution should be clear and colorless. Visually inspect the solution for discoloration and particulate matter before administration. Kepivance should not be administered if discoloration or particulates are observed.

DO NOT FILTER the reconstituted solution during preparation or administration.

Administration of Kepivance

Kepivance should be administered by intravenous bolus injection. If heparin is used to maintain an IV line, saline should be used to rinse the line prior to and after Kepivance administration (see **PRECAUTIONS: Drug Interactions**).

HOW SUPPLIED

Kepivance is supplied in vials containing 6.25 mg of palifermin.

Kepivance is supplied in a dispensing pack containing 6 single-use vials
(NDC 55513-520-06) or in a distribution case containing 4 dispensing packs
(NDC 55513-520-06) [4 x 6 vial dispensing packs (24 x 6.25 mg/vial)].

The dispensing pack containing Kepivance lyophilized powder should be stored in its carton and refrigerated at 2º to 8ºC (36º to 46ºF). PROTECT FROM LIGHT. Keep vials in pack until time of use.

REFERENCES

1. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. *Cancer*. 1981;47:207-214.

[Amgen Logo]

Kepivance® (palifermin)

Manufactured by:

Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.
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USA

Certain manufacturing operations have been performed by other firms.

This product, its production and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,420,531 B1; 5,814,605; 5,824,643; and 5,677,278 as well as other patents or patents pending.

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